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UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte
CHRISTOPHER J. M. MEADE, MICHEL PAIRET,
and MICHAEL P. PIEPER

Appeal 2008-3535
Application 10/614,365
Technology Center 1600

Decided: September 29, 2008

Before TONI R. SCHEINER, DONALD E. ADAMS,
and DEMETRA J. MILLS, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a pharmaceutical composition in the form of an inhalable aerosol, solution, or suspension, comprising a combination of an anticholinergic agent and a PDE-IV inhibitor. The Examiner has rejected the claims as obvious over the prior art. We have jurisdiction under 35 U.S.C. § 6(b).

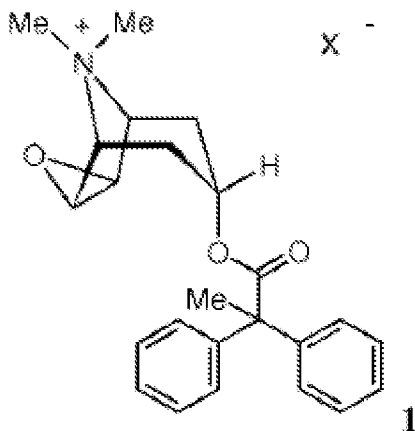
STATEMENT OF THE CASE

Claims 1, 2, 4, 5, 7-11, 13, 19-38, 43, and 44 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Knowles (International Patent application WO 03/011274 A2, published February 13, 2003), Meissner (U.S. Patent 6,706,726 B2, March 16, 2004), and Hill (U.S. Patent 6,060,069, May 9, 2000).¹

As the claims have not been argued separately, and therefore stand or fall together, we select claim 1 as representative of the claimed subject matter for the purpose of deciding all issues raised by this appeal. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 reads as follows:

1. A pharmaceutical composition, which is in the form of an inhalable aerosol, solution or suspension, comprising:

one or more anticholinergics of formula 1

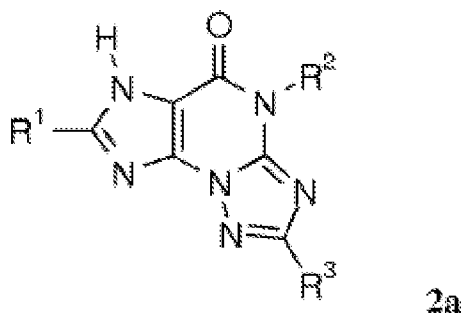


wherein

X⁻ denotes an anion with a single negative charge,

¹ The rejection of claims 1, 2, 4, 5, 7, and 43 as unpatentable under the doctrine of obviousness-type double patenting has been withdrawn by the Examiner (Ans. 3).

one or more PDE-IV inhibitors, (2), selected from enprofylline, theophylline, roflumilast, methanesulfonic acid 2-(2,4-dichlorophenylcarbonyl)-3-ureidobenzo-furan-6-yl ester, tofimilast, pumafentrine, (3-(3-cyclopentyloxy-4-methoxybenzyl)-6-ethylamino-8-isopropyl-3H purine hydrochloride), N-(3,5-dichloro-1-oxidopyridin-4-yl)-8-methoxy-2-(trifluoromethyl)quinoline-5-carboxamide, (N-(3,5-dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide), N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide and the tricyclic nitrogen heterocycles of formula **2a**



wherein

R¹ is C₁-C₅-alkyl, C₅-C₆-cycloalkyl, phenyl, benzyl or a 5- or 6-membered, saturated or unsaturated heterocyclic ring which contains one or two heteroatoms selected from oxygen and nitrogen;

R² is C₁-C₅-alkyl or C₂-C₄-alkenyl;

R³ is C₁-C₅-alkyl which is optionally substituted by C₁-C₄-alkoxy, C₅-C₆-cycloalkyl, phenoxy or a 5- or 6-membered, saturated or unsaturated heterocyclic ring which contains one or two heteroatoms selected from oxygen and nitrogen; C₅-C₆-cycloalkyl, phenyl or benzyl, each optionally substituted by C₁-C₄-alkoxy,

each optionally in the form of a racemate, an enantiomer, a diastereomer, mixtures of enantiomers or diastereomers, a tautomer, or a pharmacologically acceptable acid addition salt thereof, and

a solvent selected from the group consisting of water, ethanol and a mixture of water and ethanol.

ISSUE ON APPEAL

The Examiner contends that a composition comprising a combination of a PDE-IV inhibitor and an anticholinergic agent of formula **1** is obvious over the combination of Knowles, Meissner, and Hill.

Appellants contend that the prior art does not provide a reasonable suggestion to one of ordinary skill in the art to substitute Meissner's anticholinergic agent for Knowles' anticholinergic agent in Knowles' composition, nor does the art provide a reasonable expectation of success.

Thus, the issue on Appeal is whether the Examiner has set forth a prima facie case that the claims on appeal are obvious over the combination of Knowles, Meissner, and Hill.

FINDINGS OF FACT

FF1 The present invention is directed to an inhalable composition comprising a combination of a PDE IV (phosphodiesterase IV) inhibitor and an anticholinergic agent of formula **1**.

FF2 Knowles teaches that it is "useful to combine therapies" in treating pulmonary diseases (Knowles 2: 8), because "multiple mediators are responsible for the development of . . . [pulmonary] disease" and it is "unlikely that eliminating the effects of a single mediator could have a substantial effect on all other components of a particular pulmonary disease" (Knowles 1: 10-12).

FF3 As an "alternative to the 'mediator approach' (Knowles 1: 12-13), Knowles "regulate[s] the activity of the cells responsible for the pathophysiology of the disease" (Knowles 1: 13-14), using a "combination of a PDE 4 inhibitor and an appropriate anticholinergic agent for treating

pulmonary diseases, particularly chronic obstructive pulmonary disease (COPD), [and] asthma” (Knowles 2: 10-12).

FF4 Knowles “[e]xemplary [anticholinergic] compounds are the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, [and] hyoscyamine” (Knowles 5: 3-5), as well as tiotropium bromide (Knowles 10, Example 1B).

FF5 Knowles describes inhalable formulations comprising cilomilast (a PDE 4 inhibitor) in combination with tiotropium bromide (an anticholinergic agent) (Knowles 10, Example 1B, Tables 2, 3).

FF6 The Examiner finds that Knowles “does not disclose a pharmaceutical combination comprising [formula] 1 and a PDE-4 inhibitor” (Ans. 5).

FF7 Meissner teaches that “[a]nticholinergics may be used to therapeutic effect in . . . the treatment of asthma or COPD (chronic obstructive pulmonary disease)” (Meissner, col. 1, ll. 34-37).

FF8 The Examiner finds that Meissner “discloses anticholinergic compounds of a general formula which includes [formula] 1 as an embodiment” (Ans. 5).

FF9 Meissner teaches that “[i]t is particularly desirable to prepare a pharmaceutical composition which can be used therapeutically by administration once a day (single dose)” for treating chronic diseases (Meissner, col. 1, ll. 52-55). “The use of a drug once a day has the advantage that the patient can become accustomed . . . to regularly taking the drug” (Meissner, col. 1, ll. 55-57).

FF10 Meissner teaches that certain anticholinergic agents, “inter alia, benzilic acid esters of scoline, tropenol or tropine” (Meissner, col. 1, ll. 43-44), “[b]ecause of their extremely long period of activity, which significantly exceeds the . . . period of about one day, . . . cannot be used therapeutically for administration in a single dose per day” (Meissner, col. 2, ll. 6-10).

FF11 According to Appellants, these benzilic acid esters of scoline, tropenol, and tropine are the same “type disclosed as anticholinergics in Knowles” (App. Br. 8).

FF12 In contrast to the benzilic acid esters of scoline, tropenol and tropine, Meissner’s anticholinergic agents have “a relative rapid onset of activity” and a “duration of activity [which] does not substantially exceed a period of about one day in therapeutically beneficial doses” (Meissner 2: 16-22). Thus, Meissner’s anticholinergic agents, “by virtue of their activity profile, make it possible to prepare a drug for administration once a day” (Meissner 2, ll. 13-15).

FF13 Meissner’s shorter acting, once-a-day anticholinergics “are preferably used . . . [in] the treatment of asthma or COPD” (Meissner, col. 19, ll. 62-65).

DISCUSSION

The Examiner rejected claims 1, 2, 4, 5, 7-11, 13, 19-38, 43, and 44 under 35 U.S.C. § 103(a) as unpatentable over Knowles, Meissner, and Hill.²

² Appellants take no issue with the Examiner’s interpretation of, or reliance on Hill, and the reference is not relevant to Appellants’ arguments, so we have not discussed the reference here.

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

Often, it will be necessary . . . to look to interrelated teachings of multiple [references]; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed.

KSR Int’l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1740-41 (2007), taking into account “the inferences and creative steps that a person of ordinary skill in the art would employ” (*id.* at 1741). Moreover, “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results” (*id.* at 1739).

There is no dispute that Meissner’s formula 1 “encompasses formula 1 of appellants’ claim 1 and the compound shown in Meissner’s Example 1 is within the scope of formula 1 of appellants’ claim” (App. Br. 4-5, **FF5**).

Given Knowles teaching that pulmonary diseases like asthma and COPD are best treated with a combination of a PDE 4 inhibitor and an anticholinergic agent (**FF2, 3**), Meissner’s teaching that anticholinergics in general, and anticholinergics encompassing Appellants’ formula 1 in particular (**FF8**), are useful in the treatment of asthma and COPD (**FF7, 13**), and Meissner’s teaching that Meissner’s anticholinergics (which encompass

Appellants' formula 1) are advantageous because they can be administered once a day, while the anticholinergics disclosed by Knowles cannot (FF9, 10, 11, 12), we agree with the Examiner's conclusion that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to produce a composition . . . comprising the anticholinergic drug of Meissner . . . in place of the anticholinergics disclosed by Knowles" (Ans. 6). We are not persuaded otherwise by Appellants' arguments.

Appellants essentially contend that Knowles' anticholinergics are not "sufficiently closely structurally similar to appellants' formula 1 compound that one of ordinary skill in the art would reasonably expect them to have the same or similar properties and be interchangeable" (App. Br. 6). However, even if were to accept for the sake of argument that there are "five significant structural differences between these compounds" (*id.* at 5), mere structural similarity is not the sole basis for the Examiner's rejection. As pointed out by the Examiner, and supported by the evidence of record, "both the compounds disclosed in Knowles and those described by Meissner are disclosed as anticholinergic agents" (Ans. 9), and "both references describe the disclosed compounds and compositions as being useful for treating the same disorders, notably asthma and chronic obstructive pulmonary disease" (*id.*).

Appellants further contend that "Meissner refers to compounds of the type disclosed as anticholinergics in Knowles - i.e., benzilic acid esters - in its Background section . . . and discloses that such compounds are deficient in meeting the requirements desired for the Meissner invention. Thus, Meissner's invention was purposefully directed to structurally distinct

[anticholinergic] compounds with distinct properties” (App. Br. 8). But the premise of the Examiner’s rejection is *not* that it would have been obvious for one of skill in the art to use Knowles’ compounds in place of Meissner’s; rather, the Examiner’s rationale is that it would have been obvious to replace Knowles’ anticholinergics with Meissner’s. We agree with the Examiner that Meissner’s teaching that Knowles’ benzoic acid esters are unsuitable for once a day formulations (**FF10, 11, 12**), “provides a clear motivation for substituting the superior compound [of Meissner] for the inferior compound [of Knowles]” (Ans. 10).

Finally, Appellants contend that “obviousness cannot simply be based on the fact that Knowles and Meissner both use the term ‘anticholinergic’ and an assumption . . . that those terms were used in the same way in each reference” (Reply Br. 2). Appellants argue that “[t]here is no basis on the record to reasonably conclude that the ‘new anticholinergics’ described by Meissner . . . are of the type of anticholinergic taught to be useful for the purposes of Knowles’ invention” (*id.*). We disagree. As the Examiner has pointed out, “both references describe the disclosed compounds and compositions as being useful for treating the same disorders, notably asthma and chronic obstructive pulmonary disease” (Ans. 9).

Having considered the respective positions of Appellants and the Examiner, we find that the Examiner has established by a preponderance of the evidence that the claimed invention would have been obvious over the prior art. Appellants have not overcome the Examiner’s *prima facie* case by argument or evidence. We therefore affirm the Examiner’s rejection of the claims as unpatentable over Knowles, Meissner, and Hill.

SUMMARY

The rejection of claims 1, 2, 4, 5, 7-11, 13, 19-38, 43, and 44 under 35 U.S.C. § 103(a) as unpatentable over Knowles, Meissner, and Hill is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

cdc

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